Appl. No. 09/723,752 Amdt. dated July 17, 2003 Response to Office Action mailed on January 17, 2003

## Clean Set of All Pending Claims

(July 17, 2003)

- 43. (Currently amended) A method for inhibiting VEGF-induced angiogenesis in a subject, comprising administering to said subject an effective amount of a humanized anti-VEGF antibody which (a) binds human VEGF with a K<sub>d</sub> value of no more than about 1 x 10<sup>-8</sup>M; (b) has an ED50 value of no more than about 5nM for inhibiting VEGF-induced proliferation of endothelial cells *in vitro*; and (c) inhibits VEGF-induced angiogenesis *in vivo*, wherein 5mg/kg of said humanized antibody inhibits at least about 50% of tumor growth in an A673 *in vivo* tumor model.
- 44. (Currently amended) The method of claim 43, wherein said humanized anti-VEGF antibody binds human VEGF with a  $K_d$  value of no more than about 1 x  $10^{-9}$ M.
- 45. (Previously presented) The method of claim 43, wherein said subject has a tumor.
- 46. (Currently amended) The method of claim 45, wherein 5mg/kg of said humanized antibody inhibits at least about 80% of tumor growth in an A673 *in vivo* tumor model.
- 47. (Currently amended) The method of claim 43, said humanized anti-VEGF antibody having a heavy chain and a light chain, wherein the heavy chain variable domain comprises four framework regions (FR) and three complementarity determining regions (CDR) as a contiguous sequence represented by the formula: FR1-CDRH1-FR2-CDRH2-FR3-CDRH3-FR4, wherein the four FRs are derived from a consensus human antibody heavy chain framework region sequence and the three CDRs are derived from a non-human anti-VEGF antibody, and wherein the light chain variable domain comprises four FRs and three CDRs as a contiguous sequence represented by the formula: FR1-CDRL1-FR2-CDRL2-FR3-CDRL3-FR4, wherein the four FRs are derived from a consensus human antibody light chain framework region sequence and the three CDRs are derived from the non-human anti-VEGF antibody.
- 49. (Currently amended) The method of claim 47, wherein the heavy chain variable domain comprises the following CDR amino acid sequences: CDRH1 (GYX<sub>1</sub>FTX<sub>2</sub>YGMN, wherein  $X_1$  is T or D and  $X_2$  is N or H; SEQ ID NO: 128), CDRH2 (WINTYTGEPTYAADFKR; SEQ ID

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NO:2) and CDRH3 (YPX<sub>1</sub>YYGX<sub>2</sub>SHWYFDV, wherein X<sub>1</sub> is Y or H and X<sub>2</sub> is S or T; SEQ ID NO: 129); and wherein the light chain variable domain comprises the following CDR amino acid sequences: CDRL1 (SASQDISNYLN; SEQ ID NO:4), CDRL2 (FTSSLHS SEQ ID NO:5) and CDRL3 (QQYSTVPWT; SEQ ID NO:6).

- 50. (Currently amended) The method of claim 47, wherein the heavy chain variable domain comprises the following CDR amino acid sequences: CDRH1 (GYTFTNYGMN; SEQ ID NO:1), CDRH2 (WINTYTGEPTYAADFKR; SEQ ID NO:2) and CDRH3 (YPHYYGSSHWYFDV; SEQ ID NO:3); and wherein the light chain variable domain comprises the following CDR amino acid sequences: CDRL1 (SASQDISNYLN; SEQ ID NO:4), CDRL2 (FTSSLHS SEQ ID NO:5) and CDRL3 (QQYSTVPWT; SEQ ID NO:6).
- 51. (Currently amended) A method for inhibiting VEGF-induced angiogenesis in a subject, comprising administering to said subject an effective amount of a humanized anti-VEGF antibody which binds human VEGF with a K<sub>d</sub> value of no more than about 1 x 10<sup>-8</sup>M, said humanized anti-VEGF antibody comprising a heavy chain variable domain sequence of SEQ ID NO:116 and a light chain variable domain sequence of SEQ ID NO:115.
- 52. (Currently amended) A method for inhibiting VEGF-induced angiogenesis in a subject, comprising administering to said subject an effective amount of a humanized anti-VEGF antibody which binds human VEGF with a K<sub>d</sub> value of no more than about 1 x 10<sup>-8</sup>M, said humanized anti-VEGF antibody comprising a heavy chain variable domain sequence of SEQ ID NO:7 and a light chain variable domain sequence of SEQ ID NO:8.
- 53. (Previously presented) The method of claim 43, wherein said humanized anti-VEGF antibody is a full length antibody.
- 54. (Previously presented) The method of claim 53, wherein said humanized anti-VEGF antibody is a human IgG.
- 55. (Previously presented) The method of claim 43, wherein said humanized anti-VEGF antibody is an antibody fragment.

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- 56. (Previously presented) The method of claim 55, wherein said humanized anti-VEGF antibody is a Fab.
- 57. (Previously presented) The method of claim 43, wherein said subject has a retinal disease.
- 58. (Previously presented) The method of claim 57, wherein said retinal disease is agerelated macular degeneration (AMD).
- 59. (Previously presented) The method of claim 58, wherein the humanized anti-VEGF antibody is administered to the subject at a dose of at least about 0.5mg/kg.
- 60. (New) The method of claim 47, wherein the heavy chain variable domain FR has at least one substitution wherein the human FR residue is replaced by a corresponding residue from the non-human anti-VEGF antibody, said residue is selected from the following positions: 37H, 49H, 67H, 69H, 71H, 73H, 75H, 76H, 78H and 94H; and wherein the light chain variable domain FR has at least one substitution wherein the human FR residue is replaced by a corresponding residue from the non-human anti-VEGF antibody, said residue is selected from the following positions: 4L, 46L and 71L (positions according to Kabat numbering).